AUSTRALIA

Patents Act 1990

IN THE MATTER OF Australian Patent Application Serial No 696764 by Human Genome Sciences, Inc.

-and-

IN THE MATTER OF Opposition thereto by Ludwig Institute for Cancer Research

STATUTORY DECLARATION

I, Kari Alitalo of The Molecular/Cancer Biology Laboratory, Haartman Institute, University of Helsinki, SF-00014 Helsinki, Finland do solemnly and sincerely declare as follows :

Introduction

1. Background

I am presently working as Research Professor with The Finnish Medical Research Council of the Finnish Academy of Sciences. Since receiving my M.D. and M.Sc.D. in 1977 and 1980, respectively, from the University of Helsinki, I have worked substantially continuously as a professor and scientific researcher in Finland in areas of cellular and molecular biology and cancer research. My research has included substantial studies and explorations in fields of cancer, cancer metastasis, angiogenesis, lymphangiogenesis, and other areas related to angiogenesis. In addition to my own research efforts and my collaborations with others, I receive numerous invitations to speak at national and international symposiums in these areas of study, I supervise post-graduate research of others, I have authored and co-authored numerous original research articles published in peer-reviewed journals, and I have served on the editorial board of such journals. My detailed *curriculum vitae* is attached hereto as Exhibit 1.

1.2 I have conducted and collaborated in substantial research relating to a growth factor gene and protein that my laboratory calls "Vascular Endothelial Growth Factor C" or "VEGF-C." My attached *curriculum vitae* shows that I have co-authored several publications in peer-reviewed journals relating to the VEGF-C gene and protein, its synthesis and processing in cells, and its biological activities *in vitro* and *in vivo*. Among these publications are the following:

> **Document D70**: Joukov et al., "A Novel Vascular Endothelial Growth Factor, VEGF-C, Is a Ligand for the Flt4 (VEGFR-3) and KDR (VEGFR-2) Receptor Tyrosine Kinases," *EMBO J., 15(2)*: 290-298 (1996).
>
> **Document D71**: Joukov et al., "Proteolytic Processing regulates receptor specificity and activity of VEGF-C," EMBO J., 16(13): 3898-3911 (1997)
>
> **Document D74**: Kukk et al., "VEGF-C receptor binding and pattern of expression with VEGFR-3 suggests a role in lymphatic vascular development," *Development, 122*: 3829-37 (1996).

I also have filed patent applications relating to VEGF-C, VEGF-C variants, and uses thereof. Among these applications are the following applications:

> **Document D72**: International Patent Application No. PCT/FI96/00427, filed on 1 August 1996 by Helsinki University Licensing Ltd Oy (WO 97/05250).
>
> **Document D73**: International Patent Application No. PCT/US98/01973, filed on 2 February 1998 by Ludwig Institute for Cancer Research et al. (WO 98/33917).

Thus, my laboratory and my collaborators have substantial expertise and experience working with and expressing the VEGF-C gene and protein.

1.3 I am familiar with the opposition filed by Ludwig Institute for Cancer Research ("Ludwig Institute") to the issuance of a patent to Human Genome Sciences, Inc., ("HGS") based on HGS's Australian Patent Application No. 696764 ("the opposed application"). Ludwig Institute asked me to perform a protein expression study that may be relevant to the opposition, and provide this declaration in which I report the study and the results.

1.4 In making this declaration to the Australian Patent Office, I understand that I have an overriding duty to the Patent Office (and to any Australian Federal Court that should review the Patent Office decision) to provide objective scientific analysis that I believe to be truthful. I hereby affirm that, to the best of my knowledge and belief, factual statements herein are true and opinion statements herein represent my objective scientific opinion and analysis.

II. VEGF2 and VEGF-C

2.1 The human growth factor which my laboratory and others in the scientific community call "VEGF-C" is encoded by a human gene having 419 codons. The coding sequence of a VEGF-C cDNA may be found in **Document D73** or in the publicly accessible Genbank database under Accession No. X94216.

2.2 The 350 amino acid VEGF-2 polypeptide sequence disclosed in the opposed application of Human Genome Sciences, entitled "Vascular Endothelial Growth Factor 2" (VEGF-2(HGS)) corresponds to amino acid residues 70 to 419 of human VEGF-C (Genbank Accession No. X94216), with the exception of a single amino acid difference (Lys/Gln) at position 414 of the VEGF-C sequence.[1] HGS subsequently filed a later patent application that contained a 419 amino acid "full length" VEGF2 sequence. (See, e.g., Fig 1A-1E of **Document D44** (WO 96/39515)) The 419 residue VEGF-C and VEGF2 sequences are identical except for two amino acid differences: one at position 3 (Leu/Ser), and another at position 414 (Lys/Gln) of the VEGF-C sequence. Thus, my experience working with VEGF-C is applicable to working with VEGF2.

III. Signal Peptides

[1] The opposed patent application actually contains sequence ambiguities. If one compares the VEGF-C sequence with the VEGF2 sequence in the Sequence Listing of the opposed application, one observes amino acid differences at residue 73 and 414, and an insertion of an extra Cys residue in the VEGF2 sequence at a location between residues 369 and 370 of the 419 residue VEGF-C sequence. Based on HGS's later filed patent applications, I have concluded that the VEGF2 sequences in the figures were more appropriate to use in the experiments described herein.

3.1 Polypeptides such as growth factors that are destined for extracellular secretion are first synthesized in the cellular cytoplasm. Such polypeptides generally include a short secretory signal peptide at their amino terminus that is usually cleaved off, but serves as a vital signal to direct the nascent polypeptide into the cell's protein secretion apparatus.

3.2 Scientific experiments in my laboratory has determined that the first approximately 31 amino acids from the 419 amino acid form of VEGF-C serve as a signal peptide. The experimental details and evidence underlying this determination are reported in **Document D71.**

3.3 In the opposed patent application, the 350 amino acid VEGF2 sequence is lacking the 31 amino acids that represent the VEGF-C signal peptide. In the application, the inventors assert that the first 24 amino acids of their VEGF2 sequence (which would approximately correspond to amino acids 70-93 of the full-length 419 amino acid VEGF-C sequence) operate as a signal peptide.

Experimental Purpose

4.1 In view of my laboratory's expertise in expressing and working with the VEGF-C gene and protein, the Ludwig Institute asked me to perform experiments to determine whether or not the 350 amino acid protein contains an operative signal peptide, as alleged in the opposed application.

Experimental Design

I. Overview

5.1 The accumulated knowledge of molecular biologists regarding signal peptides have permitted biologists to identify certain characteristic features of signal peptides. (One such feature is an amino acid composition comprising largely hydrophobic residues.) Computer programs have been designed to predict whether an amino acid sequence begins with a signal peptide, and to identify the site in an amino acid sequence where a putative signal peptide is cleaved. As a first part of my analysis, I used one such

program, the SignalP program at the Center for Biological Sequence Analysis, The Technical University of Denmark, to analyze the approximately 350 amino acid VEGF2 sequence for a series of residues having characteristics of a signal sequence.

5.2. As a second part of my analysis, I transformed a mammalian cell line with an expression vector containing a polynucleotide that encodes the 350 amino acid VEGF2 sequence ("VEGF2(HGS)"), grew the cell line under conditions in which the cells produce polypeptides, and then assayed the growth medium of the cells to determine whether the cells were secreting VEGF2. These experiments included various experimental controls to assure that there was no problem with the expression vector, the cells, the transformation procedures, the growth conditions, or other parameters. The actual details of the experimental protocol are described in the next section.

II. Detailed Experimental Protocol

6.1 To determine whether eukcaryotic cells can express and secrete VEGF2(HGS), an expression plasmid containing a VEGF2(HGS) polynucleotide sequence was constructed. This involved preparing a VEGF2(HGS) DNA fragment, and inserting the fragment into a commercial expression vector.

6.1.1 The polymerase chain reaction (PCR) was employed to construct a DNA fragment that encodes amino acids 70 to 419 of VEGF-C, followed by a short hemagglutinin (HA) tag fused in-frame to the 3' end of the VEGF-C coding region.[2] The 5'-primer used in the PCR reaction contained a BamHI restriction endonuclease recognition site followed by the first 18 nucleotides from the VEGF-C(70-419) coding sequence. The 3'-primer contained an XbaI recognition

[2] As explained above, amino acids 70-419 of VEGF-C differ at position 414 from the VEGF2(HGS) amino acid sequence presented in the figures of the opposed patent. Since any signal peptide in VEGF2(HGS) would occur at the *beginning* (amino terminus) of the VEGF2(HGS) sequence, a single change at position 414, and the inclusion of a HA-tag at the end (carboxy terminus) are inconsequential to this expression study. These assumptions are verified by the VEGF-C positive control that was included in these experiments, and by the ability of my laboratory and many other laboratories to recombinantly express other polypeptides with a carboxy terminal HA tag to facilitate purification.

site, an HA-tag, a stop codon, and the last 15 nucleotides from the VEGF-C(70-419) coding region, excluding the stop codon. The locations of the 5' and 3' primers with respect to the complete VEGF-C cDNAsequence (which was used as PCR template DNA), are shown in Exhibit 2 attached hereto.

6.1.2 The resulting PCR product was digested with BamHI and XbaI and inserted into the multiple cloning site of the commercially available expression vector pcDNA1/Amp (Invitrogen) that had been digested with the same enzymes. This construct was named VEGF2(HGS)/pcDNA1, and DNA sequencing was performed to confirm that the VEGF2(HGS) insert was present and in the correct orientation for expression.

6.1.3 To serve as an experimental control, a similar expression plasmid, designated VEGF-C/pcDNA1 was also constructed. In this expression plasmid, a DNA encoding the complete 419 amino acid VEGF-C polypeptide was cloned into pcDNA1.

6.2 The 293T mammalian cell line was selected for the expression study. Thus, 293T cells, grown in DMEM medium supplemented with 10% fetal bovine serum, glutamine and penicillin/streptomycin, were mock-transfected (control), transiently transfected with VEGF2(HGS)/pcDNA1, or transiently transfected with VEGF-C/pcDNA1 using the calcium-phosphate method.

6.3 Radioactive amino acids that would be incorporated into nascent polypeptides were introduced into the cell growth medium to assist in the identification of expressed polypeptides. In particular, 48 hours after transfection, the transfected cells were washed twice with phosphate-buffered saline (PBS) and metabolically labeled in MEM medium containing 100μCi/ml ^{35}S-methonine and ^{35}S-cysteine (Promix, Amersham) for 6 hours. The conditioned media was harvested and cleared of contaminants by centrifugation. After washing three times with ice cold PBS, the cells were lysed in ice cold RIPA-buffer

(150 mM NaCl, 1% NP-40, 0.5% DOC, 0.1% SDS, 50 mM Tris); supplemented with 0.01 U/ml aprotinin, 1μg/ml leupeptin, and 1mM PMSF; and the lysate was cleared by centrifugation.

6.4 Before analysis for expressed VEGF2(HGS) and VEGF-C, steps were taken to assure that any low levels of VEGF produced by 293T cells would not confound the results. Endogenous VEGF was removed from the conditioned media and cell lysates by incubation with 1 μg/ml monoclonal anti-human VEGF antibody (R & D Systems), followed by precipitation of the immunocomplexes with protein A-Sepharose (Amersham Pharmacia Biotech).

6.5 Next, an immunoprecipitation was conducted to capture any VEGF2(HGS) or VEGF-C from the conditioned media or cell lysates. For immunoprecipitation, the conditioned media was supplemented with BSA, Tween 20, and heparin to final concentrations of 0.5%, 0.02%, and 1 μg/ml, respectively. VEGF2(HGS) was immunoprecipitated at 4 C with 4 μg/ml monoclonal anti-HA antibody (HA.11, BabCO), and VEGF-C was immunoprecipitated at 4 C with 882 antiserum, a polyclonal antibody raised against a synthetic peptide corresponding to residues 35-51 of the 350 amino acid VEGF2 polypeptide. The immunocomplexes were collected on protein A-Sepharose and washed twice with 1X binding buffer (0.5% BSA, 0.02% Tween 20, 1 μg/ml heparin), and once with 20 mM TrisHCl pH 7.4 at 4 C. The proteins were analyzed on 15% SDS-PAGE under reducing conditions.

Experimental Results

7.1 Analysis of the VEGF2(HGS) sequence with the SignalP program indicated that this 350 amino acid sequence does not begin with a sequence having hydrophobicity characteristics of a signal sequence.

7.2 An autoradiogram of the SDS-PAGE gel is attached hereto as Exhibit 3. That exhibit shows that the VEGF2(HGS) polypeptide is detected in cell lysates (lane 4), but not

conditioned media (lane 1), from 293T cells transfected with VEGF2(HGS)/pcDNA1. In contrast, VEGF-C polypeptide was detected in both cell lysates (lane 5) and conditioned media (lane 2) from 293T cells transfected with VEGF-C/pcDNA1. VEGF2(HGS) detected in cell lysates migrates as a circa 46 kD protein, whereas the majority of VEGF-C detected in the conditioned media migrated as a broad doublet band of approximately 29-31 kD polypeptides and another band of about 21 kD. A significant quantity of higher molecular weight polypeptides were observed in the cell lysates of the VEGF-C-transfected cells, which I interpret as VEGF-C "captured" at various stages of proteolytic processing[3] (as a result of lysing the cells six hours after labeling. In addition, it is readily apparent from the autoradiogram that the expression level of VEGF-C is much higher than that of VEGF2(HGS).

Analysis

8.1 If VEGF2(HGS)-transfected cells had secreted any VEGF2(HGS) protein, the protein would have been captured by the anti-HA antibody and visualized in the conditioned medium from these cells (Exhibit 3, lane 1). No VEGF2(HGS) was observed in this lane, indicating that no VEGF2(HGS) secretion was occurring. Thus, I conclude that the 350 amino acid VEGF2 sequence taught in the opposed application does NOT contain a signal peptide sequence. This conclusion is further supported by the computer analysis which failed to identify any sequence in the 350 residue VEGF2 that has hydrophobicity characteristics of a signal peptide.

8.2 The experimental procedures were sound, as evinced by the high level of secreted VEGF-C that was observed in the conditioned media of cells that had been transfected with the full-length VEGF-C cDNA construct (lane 2), and the observation of a well-defined, unsecreted 46 kD polypeptide band captured by the anti-HA antibody from the cell lysate of VEGF2(HGS)-transfected cells.

[3] A detailed description of VEGF-C proteolytic processing is set forth in Document D71, which I incorporate herein by reference.

8.3 The fact that VEGF-C expression observable in cell lysates of VEGF-C-transfected cells is much higher than VEGF2(HGS) expression observable in VEGF2(HGS)-transfected cells suggests that VEGF2(HGS) is inefficiently translated and/or that the intracellular turnover rate of VEGF2(HGS) is much faster than that of VEGF-C. In other words, the cells may be recognizing VEGF2(HGS) as an aberrant protein and rapidly degrading it.

Summary

9.1 The failure of cells transfected with an expression vector containing the 350 amino acid VEGF2 cDNA sequence taught in the opposed patent application to secrete any VEGF2 protein indicates that the 350 amino acid VEGF2 cDNA sequence taught in the opposed application does not contain a functional signal peptide, as the patent applicants allege.

AND I MAKE this solemn declaration by virtue of the Statutory Declarations Act 1959, and subject to the penalties provided by that Act for the making of false statements in statutory declarations, conscientiously believing the statements contained in this declaration to be true in ev[illegible] particular.

DECLARED at Helsinki

this 15th day of February 2000

Kari Alitalo

BEFORE ME:

OLLI-PEKKA SIRO
Notary Public
Notary Public

AUSTRALIA

Patents Act 1990

IN THE MATTER OF Australian Patent Application Serial No 696764 by Human Genome Sciences, Inc.

-and-

IN THE MATTER OF Opposition thereto by Ludwig Institute for Cancer Research

THIS IS Exhibit 1 referred to in the Statutory Declaration of Kari Alitalo made before me this 15th Day of February, 2000

OLLI-PEKKA SIRO
Notary Public

HELSINGIN MAISTRAATTI
MAGISTRATEN I HELSINGFORS

CURRICULUM VITAE

Kari Kustaa Alitalo, born 21.05.52

Position:

Research Professor, the Finnish Medical Research Council of the Finnish Academy of Sciences
1.8.1993-31.7.2003

Education:

Educational Commission for Foreign Medical Graduates (USA) - exam	1976
M.D.University of Helsinki	1977
M.Sc.D. (basic sciences, corresponding to Ph.D. degree) University of Helsinki	1980

Previous professional appointments:

Research and teaching assistantships, Departments of Pathology, Virology, State Medical Research Council, The Finnish Academy of Sciences	1977-1982
Visiting Scientist, Department of Biochemistry, University of Washington, Seattle, USA (Dr. Paul Bornstein)	1981-1982
Visiting Scientist, Department of Microbiology and Immunology, University of California, San Francisco, USA (Dr. J. Michael Bishop and Dr. Harold E. Varmus)	1982-1983
Research Fellow, Senior RF, State Medical Research Council	1983-1986
Professor of Medical Biochemistry, University of Turku	12.1986-10.1987
Research Professor, The Finnish Cancer Institute	10.1987-07.1988
Professor of Cancer Biology, University of Helsinki	07.1988-07.1993
Professor of Medical Biochemistry, University of Helsinki	10.1996-
Research Professor, the Finnish Academy of Sciences	08.1993-

Research awards and honours:

Primus Doctorum in the X Promotion of The Medical Faculty, University of Helsinki	1981
The Jahre Prize, Oslo, Norway	1987
Farmos Oy: Science Prize, Turku, Finland	1987
The Medix Prize for the Best Finnish Paper in the Biosciences in 1989	1990
The Finnish Medical Society Duodecim Äyräpää Prize	1998
The Medix Prize for the Best Finnish Paper in the Biosciences in 1997	1998
Europe Medecine Senior Prize	1999

Editorial board memberships:

EMBO Journal	1994-1998 2000-
The FASEB Journal	
International Journal of Cancer	
British Journal of Cancer	

Memberships in scientific societies:

European Molecular Biology Organization	1990-
Fund Committee	1994-1997

The Scientific Council, IARC/WHO	1991-1995
Nordic.Molecular Biology Association (NOMBA)	1995-
Executive board	1990-1992
Scientific Evaluation group, International Cancer Technology Transfer-program (UICC)	
Finnish Association of Pathology	
Executive board	1985-1992
Chairman	1989-1991
Finnish Science Academy	
Finnish Cell Biology Association	
Societas Biochemica, Biophysica et Microbiologica Fennica	
American Society of Cell Biology	
American Association for Cancer Research	

Mentor for doctoral training:

1. Robert Winqvist: Chromosomal analysis of amplified oncogenes and *myc* protein, 1986.
2. Kalle Saksela: *myc* genes in human lung cancer: regulation and amplification, 1989.
3. Lea Sistonen: Regulation of gene expression by c-Ha-*ras* and *neu* oncoproteins, 1990.
4. Heikki Lehväslaiho: Functional analysis of the *neu* oncoprotein by recombinant DNA techniques, 1991.
5. Laura Lehtola: Analysis of the *neu* oncoprotein and other tyrosine kinases expressed in breast cancer cells, 1991.
6. Päivi Koskinen: Regulation and roles of c-*myc* and other growth factor-responsive genes, 1991.
7. Tomi Mäkelä: Studies on *myc* family and associated proteins: identification of the *rlf*-L-*myc* rearrangement, 1991.
8. Juha Partanen: Molecular cloning and characterization of novel tyrosine kinases expressed in K562 human leukemia cells, 1992.
9. Elina Armstrong: Analysis of chromosomal location and expression of novel leukemia cell receptor tyrosine kinase genes, 1993.
10. Harri Hirvonen: Of Myc and Men - expression of *MYC* proto-oncogenes in human fetal development, leukemias and brain tumors, 1993.
11. Liisa Pertovaara: Gene regulation by transforming growth factor-ß and inducers of tumor cell differentiation, 1994.
12. Jaana Korhonen: Characterization of endothelial receptor tyrosine kinases Tie and Flt4 in angiogenesis, 1995.
13. Katri Pajusola: Cloning and characterization of a new endothelial receptor tyrosine kinase Flt-4 and two novel VEGF-like growth factors VEGF-B and VEGF-C, 1996.
14. Imre Västrik: Max, ΔMax and Mad1 as regulations of Myc proteins, 1996.
15. Satu Vainikka: Signal Transduction and expression of FGF receptor-4, 1996.
16. Erika Hatva: Receptor tyrosine kinases and growth factors in human brain tumors and vascular malformations, 1996.
17. Arja Kaipainen: Molecular control of lymphangiogenesis: Role of VEGF-C and its receptors, 1997.
18. Juha Klefström: Oncogenes as regulators of tumor necrosis factor induced cell death, 1997.
19. Petri Salven: Angiogenic molecules and cancer. Role of the vascular endothelial growth factor family, 1998.
20. Birgitta Olofsson: Studies of the vascular endothelial growth factors, VEGFs, and their receptors focusing on VEGF-B, 1999.
21. Athina Lymboussakis: Vascular endothelial growth factors and their receptors in embryos, adults and tumors, 1999.

Invited speaker:

Recombinant DNA applications to defects in cellular functions and human diseases, 12.- 14.05.1985, Gentofte, ***Denmark***
Acta Endocrinologica Congress, 4.-10.08.1985, Helsinki, ***Finland***
EMBO Workshop on Oncogenes and Immortalization 4.-07.09.1985, Grignon, ***France***
Meeting of the Nordic Study Group on Cellular and Chemical Carcinogenesis, 14.-17.10.1985, Gl. Vrå, ***Denmark***
Maimonides Conference on Cancer Research, 1.-7.12.1985, Ein Gedi, ***Israel***
Chairman of the meeting "Role of Oncogenes in Human Cancer", 9.-10.01.1986, Helsinki, ***Finland***
European Tumor Virus Group Meeting, Chairman of the session "Cellular Oncogenes", 12.-19.04.1986, Le Normont, ***France***
Growth Factror Cascades: Mechanisms and opportunities for intervention, 15.-16.6.1986, Oslo, ***Norway***
Virus, Oncogenes et Cancer Humain, 21.4.1986, Villejuif, ***France***
IXV Annual Meeting of the International Society for Oncodevelopmental Biology and Medicine, 14.-17.08.1986, Helsinki, ***Finland***
Recombinant DNA in Clinical Medicine, 23.-26.8.1986, Hanasaari ***Finland***
First Conference on Differentiation Therapy 30.8.-3.9.1986, Capo Boi, ***Italy***
Cancer Prevention: Basic and Practical, 18.-19.10.1986, Hanasaari, ***Finland***
Growth Factors, Oncogenes and Cancer 22.-26.10.1986, Stockholm, ***Sweden***
EMBO Symposium on Oncogenes and Growth Control, 26.-30.4.1987, Heidelberg, ***Germany***
IX Meeting of the European Association for Cancer Research, 1.-3.6.1987, Helsinki, ***Finland***
Expression of Oncogenes and Regulation of Cell Growth, 5.-6.6.1987, Uppsala, ***Sweden***
Tumor Biology, Karolinska Institutet, 19.-20.8.1987, Stockholm, ***Sweden***
EACR Workshop on Oncogene Expression in Human Tumours 2.-4.9.1987, Cambridge, ***UK***
XII Berzelius Symposium: Growth Factors and Oncogenes – Structure, Function and Clinical Implications, 7.-8.9.1987, Sigtuna, ***Sweden***
Directions in Bioscience 11.-15.4.1988, Newark, ***USA***
XXI Nordiska Kongressen I Klinisk Kemi: Growth factors, oncogenes and cancer, 19.-22.6.1988, Kuopio, ***Finland***
European Tumor Virus Group Meeting, 30.4.-5.5.1989, Sundbyholm, ***Sweden***
Nordic Cancer Union Meeting, 17.-19.8.1989, Stockholm, ***Sweden***
EACR Oncogenes and Growth Control meeting 11.-12.9.1989, Galway, ***Ireland***
Molecular Basis of Human Cancer 13.-16.6.1990, Frederick, ***USA***
European Study Group on Cell Proliferation 13.9.1990, Espoo, ***Finland***
Oncogenes and Growth Control, The British Council 4.-7.6.1990, London, ***England***
Third European Congress on Cell Biology, 2.-5.9.1990, Firenze, ***Italy***
International Symposium on Angiogenesis, Chairman of the molecular biology session, 13.-15.3.1991, St. Gallen, ***Switzerland***
Scandinavian Breast Cancer Symposium 3.-5.6.1991, Haikko, ***Finland***
Sixth European Conference on Clinical Oncology and Cancer Nursing, 27.-31.10.1991, Firenze, ***Italy***
22nd Symposium of the Princess Takamatsu Cancer Research Fund, 19.-21.11.1991, Tokyo, ***Japan***
BACR Meeting on Growth Control and Cancer Therapy, 5.-7.12.1991, London, ***UK***
6th Congress of the European Society of Surgical Oncology, 10.-13.6.1992, Helsinki, ***Finland***
Growth Factor Receptors 15.-19.6.1992, Alpbach, ***Austria***
Molecular Basis of Human Cancer, 18.-21.6.1992, Frederick, ***USA***
Regulatory Peptides of the Fibroblast Growth Factor Family, 11.-16.10.1992, Roscoff, ***France***

Mutant Oncogenes: Targets for Therapy 1992, 22-23.10.1992, London, *England*
Signalling mechanisms involved in control of cell growth, 3.-4.12.1992, London, *England*
8th International Symposium on Detection and Prevention of Human Cancer, 14.-18.3.1993, Nice, *France*
Phosphorylation/Dephosphorylation in Signal Transduction, 17.-24. 1.1993, Keystone, *USA*
XII Meeting of the European Association for Cancer Research, 4.-7.4.1993, Brussels, *Belgium*
European Congress on Biotechnology, 14.-16.6.1993, Firenze, *Italy*
The Molecular Basis of Cancer, 18.-20.6,1993, Frederick, *USA*
Ninth Annual Meeting on Oncogenes, 22.-26.6.1993, Frederick, *USA*
Growth Factors and Their Receptors, 16.-18.8.1993, Uppsala, *Sweden*
Cancer Symposium, 29.8-1.9.1993, Copenhagen, *Denmark*
Lympho-Hemopoiesis, 4.-7.9.1993, Ulm, *Germany*
Regulatory Molecules in Cell Proliferation, Cell Differentiation and Apoptosis, 10.-13.10.1993, Essen, *Germany*
Banbury Meeting on Mechanisms of Developmental and Tumor Angiogenesis. 7.-10.11.1993, Cold Spring Harbor, *USA*
Interactions of Cancer Susceptibility Genes and Environmental Carcinogens, 9.-13.11.1993, Lyon, *France*
Molecular Pathobiology of Cancer, 11-15 4.1994, Dalfsen, *The Netherlands*
Molecular and Cellular Aspects of FGFs and their Receptors, 29.5.-02.6.1994, Capri, *Italy*
FEBS Special Meeting on Biological Membranes, 26.6.-1.7.1994, Helsinki, *Finland*
Regulation of Hematopoietic Stem Cells, 18.-20.12.1994, Osaka, *Japan*
Human Hematopoietic Stem Cell Meeting, 31.3.-2.4.1995, Vienna, *Austria*
Cytoplasmic Protein-Tyrosine Kinases, 12.-14.5.1995, Stockholm, *Sweden*
Chairman of the EMBO Workshop on Growth Factors and Receptor Kinases, 26.-28.5.1995, Helsinki, *Finland*
The Frontiers of Contemporary Science, 5.-7.6.1995, Kuopio, *Finland*
3rd Meeting of the Federation of European Biochemical Societies, 13.-18.8.1995, Basel, *Switzerland*
International Society of Experimental Hematology, 27.-31.8.1995, Düsseldorf, *Germany*
Tumor angiogenesis and anti-angiogenesis, 1.-5.11.1995, Titisee, *Germany*
Keystone symposium on Signal Transduction through Tyrosine Kinases, 27.3.-2.4.1996, Taos, *USA*
Vascular Endothelium and Regulation of Leukocyte Traffic, 20-22.5.1996, Madrid, *Spain*
EMBO Practical Course on Growth and Differentiation Factors, 27.7.1996, Birmingham, *England*
Fourth International Workshop on Targeted Cancer Therapy, 21.-23.8.1996, Bethesda, Maryland, *USA*
Symposium on Vascular Remodeling, 14.9.1996, Tokyo, *Japan*
IX International Vascular Biology Meeting, 4.-8.9.1996, Seattle, *USA*
First Haartman Symposium on Cell Differentiation, 19.-21.9.1996 Helsinki, *Finland*
Development, Cell Differentiation and Cancer, 28.9.-2.10.1996, Pisa, *Italy*
The Role of Cytokines in Human Disease, 17.-20.11.1996, Tegernsee, *Germany*
AACR Conference on Cell Signalling and Cancer Treatment, 23.-28.2.1997, Telfs-Buchen, *Austria*
A lecturer of the Program of Ten-Year Cancer Control, 29.3.-6.4.1997, Tokyo, Kanazawa, Kumamoto, *Japan*
Gordon Conference on Angiogenesis and Microcirculation, 17.-22.8.1997, New Hampshire, *USA*
Wenner-Gren Symposium on Protein Phosphorylation, 4.-6.9.1997, Stockholm, *Sweden*
Cell Signaling and Tumor Angiogenesis, 9.-14.9.1997, Lake Placid, *USA*
The European Cancer Conference, 14.-18.9.1997, Hamburg, *Germany*
Philippe Laudat Conference, 21.-25.9.1997, Paris, *France*
Molecular Determinants of Cancer Metastasis, 28.-31.10.1997, Houston, *USA*
The Endothelial Cell, 14.11.1997, Paris, *France*
merican Society of Hematology Annual Meeting, 3.-11.12.1998, San Diego, *USA*

Angiogenesis and Cancer, 24.-28.1.1998, Orlando, *USA*
Signal Transduction and Angiogenesis, 5.-8.2.1998, Paris, *France*
Ovarian Cancer - Basic Science and Modern Treatment, 20.3.1998, Tampere, *Finland*
Vascular Biology of Complications in Diabetes, 5.4.1998, Stockholm, *Sweden*
IBC/Angiogenesis Meeting 24.4.1998, Boston, *USA*
Angiogenesis Meeting, 27.5.1998, London, *England*
MDC Symposium, 6th Symposium on Gene Therapy, 4.-6.5.1998, Berlin-Buch, *Germany*
Vascular Complications in Diabetes, 30.4.1998, Stockholm, *Sweden*
EFES 2nd Postgraduate Course in Molecular and Cellular Endocrinology, 8.6.1998, Turku, *Finland*
Laboratory Medicine 98, XXVI Nordic Congress of Clinical Chemistry, 8.6.1998, Turku, *Finland*
Silver Jubilee FEBS Meeting, 5.-10.7.1998, Copenhagen, *Denmark*
Vascular Biology Conference 98, 24.-25.7.1998, Ohtsu, *Japan*
Gordon Research Conference on Peptide Growth Factors, 9.-14.8.1998, New Hampshire, *USA*
Xth International Vascular Biology Meeting, 23.-27.8.1998, Cairns, *Australia*
5th Franz-Volhard-Symposium, 3.-4.9.1998, Gross Dölln, *Germany*
First International Symposium on GIST, 25.-26.9.1998, Helsinki, *Finland*
10th Conference of the International Society of Differentiation, 3.-7.10.1998, Houston, *USA*
29th International Symposium of the Princess Takamatsu Cancer Research Fund, 17.-19.11.1998, Tokyo, *Japan*
Novel tools and methologies to promote or inhibit angiogenesis for drug development, 3.-4.12.1998, London, *England*
Role vascular endothelial growth factors in normal and pathological blood vessel formation, 18.-20.12.1998, Siena, *Italy*
UK Molecular Biology and Cancer Network meeting 15, 14.-16.12.1998, Warwick, *England*
NOVO Nordisk Ceremony, 24.-25.1.1999, Copenhagen, *Denmark*
ESF/EMRC Workshop on Proteome Analysis in Medical Research, 5.-7.2.1999, Chamonix, *France*
Annual Meeting of the Center for Molecular medicine (ZMMK), Signal Transduction and Disease, 13.-14.3.1999, Cologne, *Germany*
Danish Association for Cancer Research, Annual Meeting, 22-23.4.1999, Copenhagen, *Denmark*
International Titisee Conference, Parallels in cancer and embryonic development, 29.4.-2.5.1999, Titisee-Neustadt, *Germany*
EVBA meeting, Endothelial Cell Activation: Inflammation and Angiogenesis, 15.-16.5.1999, Baden, *Austria*
Ludwig Institute for Cancer Research, Angiogenesis meeting, 7.6.1999, Helsinki, *Finland*
European Developmental Biology Congress–99, 19-23.6.1999, Oslo, *Norway*
UICC Conference on Cell Signaling and Cancer, 5.-8.8.1999, Tammsvik, *Sweden*
Gordon Conference on Angiogenesis and Microcirculation, Salve Regina University, 14.-21.8.1999, Newport, *USA*
VII Danish Cancer Society Symposium, 24.8.1999, Copenhagen, *Denmark*
The IXth Annual BioCity Symposium, From Receptor Activation to Gene Expression, 26.-27.8.1999, Turku, *Finland*
MMGM, Mouse Molecular Genetics Meeting, 4.9.1999, Heidelberg, *Germany*
European Meeting on Vascular Biology and Medicine, 29.-30.9.1999, Nürnberg, *Germany*
EMBO Workshop on Stem Cells, Growth Factors and Cancer, 7.-10.10.1999, Torino, *Italy*
IIGB Workshop on Vasculogenesis and Angiogenesis, 9.-12.10.1999, Capri, *Italy*
ESH Conference on Angiogenesis and Tumours, 22.-25.10.1999, Paris, *France*
International Society for Oncodevelopmental Biology and Medicine, 31.10.-4.11.1999, Kyoto, *Japan*
ASN Basic Science Conference, 2.-4.11.1999, Miami, *USA*
Workshop on Lymphoid Organogenesis, 5.11.1999, Basel, *Switzerland*
Biological basis for antiangiogenic therapy, 7.-10.11.1999, Milan, *Italy*

Angiogenesis Workshop, 11.11.1999, Basel, *Switzerland*
Nordic.Symposium of Radiation Oncology, 22.-24.11.1999, Tampere, *Finland*

Opponent of doctoral dissertations:

Dr. Zvi Wirschubsky, Karolinska Institutet, Stockholm, Sweden, 1986
Dr. Sigurdur Ingvarsson, Karolinska Institutet, Stockholm, Sweden, 1989
Dr. Arne Östman, University of Uppsala, Uppsala, Sweden, 1990
Dr. Klaus Elenius, University of Turku, Turku, Finland, 1992
Dr. Berthe Willumsen, University of Copenhagen, Copenhagen, Denmark,1993

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Patents

Kari Alitalo, CV and publications

United States Patent 5,607,918 Eriksson, et. al. Mar. 4, 1997 Vascularendothelial growth factor-B and DNA coding therefor Inventors: Eriksson;Ulf (B.ang.lsta, SE); Olofsson;Birgitta (Sundbyberg, SE); Alitalo; Kari (Helsinki, FI); Pajusola; Katri (Helsinki, FI). Assignee: Ludwig Institute for Cancer Research (New York, NY); Helsinki University Licensing Ltd. Oy (University of Helsinki, FI). Appl. No.: Filed: Jun. 6, 1995

nited States Patent 5,776,755 Alitalo, et. al. Jul. 7, 1998 FLT4, a receptor tyrosine kinase Inventors: Alitalo; Kari (Espoo, FI); Aprelikova; Olga (Helsinki, FI); Pajusola; Katri (Helsinki, FI); Armstrong; Elina (Helsinki, FI); Korhonen; Jaana (Helsinki, FI); Kaipainen; Arja (Helsinki, FI). Assignee: Helsinki University Licensing, Ltd. (Helsinki, FI). Filed: Nov. 14, 1994

AUSTRALIA

Patents Act 1990

IN THE MATTER OF Australian Patent Application Serial No 696764 by Human Genome Sciences, Inc.

-and-

IN THE MATTER OF Opposition thereto by Ludwig Institute for Cancer Research

THIS IS Exhibit 2 referred to in the Statutory Declaration of Kari Alitalo made before me this 15th Day of February, 2000

OLLI-PEKKA SIRO
Notary Public
Notary Public

HELSINGIN MAISTRAATTI
MAGISTRATEN I HELSINGFORS

EXHIBIT 2

Nucleotide and Amino Acid Sequence of VEGF-C and primers to make VEGF2(HGS)

The 5' and 3' primers used in the PCR reaction are indicated in capital letters. The BamHI site in the 5' primer and the XbaI site in the 3' primer are underlined. The 3' primer also encodes an HA-tag 3' to the last codon of VEGF-C (which encodes a serine), followed by a stop codon indicated in boldface.

```
ccacccctgc ccccgccagc ggaccggtcc cccacccccg gtccttccac c atg cac  357
                                                          Met His
                                                            1

ttg ctg ggc ttc ttc tct gtg gcg tgt tct ctg ctc gcc gct gcg ctg   405
Leu Leu Gly Phe Phe Ser Val Ala Cys Ser Leu Leu Ala Ala Ala Leu
          5                  10                  15

ctc ccg ggt cct cgc gag gcg ccc gcc gcc gcc gcc gcc ttc gag tcc   453
Leu Pro Gly Pro Arg Glu Ala Pro Ala Ala Ala Ala Ala Phe Glu Ser
     20                  25                  30

gga ctc gac ctc tcg gac gcg gag ccc gac gcg ggc gag gcc acg gct   501
Gly Leu Asp Leu Ser Asp Ala Glu Pro Asp Ala Gly Glu Ala Thr Ala
 35                  40                  45                  50

tat gca agc aaa gat ctg gag gag cag tta cgg tct gtg tcc agt gta   549
Tyr Ala Ser Lys Asp Leu Glu Glu Gln Leu Arg Ser Val Ser Ser Val
                55                  60                  65


5'-CGC GGA TCC ATG ACT GTA CTC TAC CCA-3' 5' Primer

gat gaa ctc atg act gta ctc tac cca gaa tat tgg aaa atg tac aag   597
Asp Glu Leu Met Thr Val Leu Tyr Pro Glu Tyr Trp Lys Met Tyr Lys
            70                  75                  80

tgt cag cta agg aaa gga ggc tgg caa cat aac aga gaa cag gcc aac   645
Cys Gln Leu Arg Lys Gly Gly Trp Gln His Asn Arg Glu Gln Ala Asn
          85                  90                  95

ctc aac tca agg aca gaa gag act ata aaa ttt gct gca gca cat tat   693
Leu Asn Ser Arg Thr Glu Glu Thr Ile Lys Phe Ala Ala Ala His Tyr
     100                 105                 110

aat aca gag atc ttg aaa agt att gat aat gag tgg aga aag act caa   741
Asn Thr Glu Ile Leu Lys Ser Ile Asp Asn Glu Trp Arg Lys Thr Gln
115                 120                 125                 130

tgc atg cca cgg gag gtg tgt ata gat gtg ggg aag gag ttt gga gtc   789
Cys Met Pro Arg Glu Val Cys Ile Asp Val Gly Lys Glu Phe Gly Val
                135                 140                 145

gcg aca aac acc ttc ttt aaa cct cca tgt gtg tcc gtc tac aga tgt   837
Ala Thr Asn Thr Phe Phe Lys Pro Pro Cys Val Ser Val Tyr Arg Cys
            150                 155                 160

ggg ggt tgc tgc aat agt gag ggg ctg cag tgc atg aac acc agc acg   885
Gly Gly Cys Cys Asn Ser Glu Gly Leu Gln Cys Met Asn Thr Ser Thr
          165                 170                 175

agc tac ctc agc aag acg tta ttt gaa att aca gtg cct ctc tct caa   933
Ser Tyr Leu Ser Lys Thr Leu Phe Glu Ile Thr Val Pro Leu Ser Gln
     180                 185                 190
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ggc ccc aaa cca gta aca atc agt ttt gcc aat cac act tcc tgc cga    981
Gly Pro Lys Pro Val Thr Ile Ser Phe Ala Asn His Thr Ser Cys Arg
195                 200                 205                 210

tgc atg tct aaa ctg gat gtt tac aga caa gtt cat tcc att att aga   1029
Cys Met Ser Lys Leu Asp Val Tyr Arg Gln Val His Ser Ile Ile Arg
                215                 220                 225

cgt tcc ctg cca gca aca cta cca cag tgt cag gca gcg aac aag acc   1077
Arg Ser Leu Pro Ala Thr Leu Pro Gln Cys Gln Ala Ala Asn Lys Thr
            230                 235                 240

tgc ccc acc aat tac atg tgg aat aat cac atc tgc aga tgc ctg gct   1125
Cys Pro Thr Asn Tyr Met Trp Asn Asn His Ile Cys Arg Cys Leu Ala
        245                 250                 255

cag gaa gat ttt atg ttt tcc tcg gat gct gga gat gac tca aca gat   1173
Gln Glu Asp Phe Met Phe Ser Ser Asp Ala Gly Asp Asp Ser Thr Asp
    260                 265                 270

gga ttc cat gac atc tgt gga cca aac aag gag ctg gat gaa gag acc   1221
Gly Phe His Asp Ile Cys Gly Pro Asn Lys Glu Leu Asp Glu Glu Thr
275                 280                 285                 290

tgt cag tgt gtc tgc aga gcg ggg ctt cgg cct gcc agc tgt gga ccc   1269
Cys Gln Cys Val Cys Arg Ala Gly Leu Arg Pro Ala Ser Cys Gly Pro
                295                 300                 305

cac aaa gaa cta gac aga aac tca tgc cag tgt gtc tgt aaa aac aaa   1317
His Lys Glu Leu Asp Arg Asn Ser Cys Gln Cys Val Cys Lys Asn Lys
            310                 315                 320

ctc ttc ccc agc caa tgt ggg gcc aac cga gaa ttt gat gaa aac aca   1365
Leu Phe Pro Ser Gln Cys Gly Ala Asn Arg Glu Phe Asp Glu Asn Thr
        325                 330                 335

tgc cag tgt gta tgt aaa aga acc tgc ccc aga aat caa ccc cta aat   1413
Cys Gln Cys Val Cys Lys Arg Thr Cys Pro Arg Asn Gln Pro Leu Asn
    340                 345                 350

cct gga aaa tgt gcc tgt gaa tgt aca gaa agt cca cag aaa tgc ttg   1461
Pro Gly Lys Cys Ala Cys Glu Cys Thr Glu Ser Pro Gln Lys Cys Leu
355                 360                 365                 370

tta aaa gga aag aag ttc cac cac caa aca tgc agc tgt tac aga cgg   1509
Leu Lys Gly Lys Lys Phe His His Gln Thr Cys Ser Cys Tyr Arg Arg
                375                 380                 385

cca tgt acg aac cgc cag aag gct tgt gag cca gga ttt tca tat agt   1557
Pro Cys Thr Asn Arg Gln Lys Ala Cys Glu Pro Gly Phe Ser Tyr Ser
            390                 395                 400

                                    3'Primer 3' TCT GGT GTT TAC

gaa gaa gtg tgt cgt tgt gtc cct tca tat tgg aaa aga cca caa atg   1605
Glu Glu Val Cys Arg Cys Val Pro Ser Tyr Trp Lys Arg Pro Gln Met
        405                 410                 415

TCG GAG CTC ATG GGT ATG CTG CAG GGT CTG ATG CGA ACT AGA TCT CGC-5'

agc taagattgta ctgttttcca gttcatcgat tttctattat ggaaaactgt        1658
Ser
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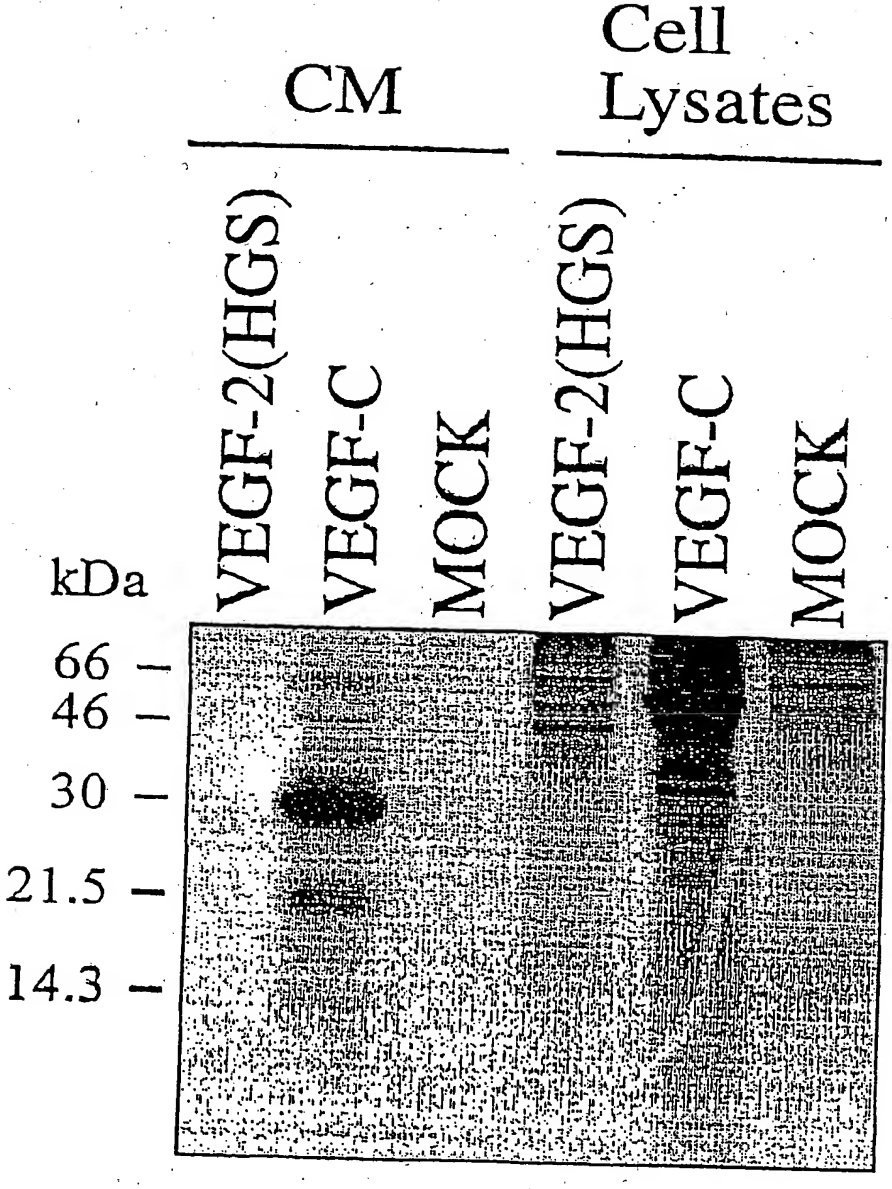
CM
Cell Lysates
VEGF-2(HGS)
VEGF-C
MOCK
VEGF-2(HGS)
VEGF-C
MOCK
kDa
66
46
30
21.5
14.3